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EXAMINER	
KHANNA, HEMANT	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/551,840	SAMARITANI ET AL.	
	Examiner	Art Unit	
	Hemant Khanna	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-107* is/are pending in the application.

4a) Of the above claim(s) *90-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-71 and 75-89* is/are rejected.

7)☒ Claim(s) *72-74* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of claims 46-107 that belong to Group I in the reply filed on September 25, 2006 is acknowledged.

The traversal is on the ground(s) that unity of invention exists between Groups I-VI because there is a technical relationship that involves the same special technical feature (Page 3, Remarks). Further, the Applicant's allege that the combination of references US '557 and US '974 would have rendered obvious the claims, lacks support.

The restriction for Groups I-VI is maintained. The Applicant's arguments are not found persuasive. While the Applicant's allege that there is a technical relationship between Groups I-VI, the Applicant's have failed to define the same special technical feature that makes a contribution over the prior art cited by the Examiner. Further, the Examiner respectfully argues that the claims and species do not fall within the unity of invention requirements of the PCT rule in as much as the common technical feature is a combination of the follicle stimulating hormone and the surfactant PLURONIC F68, since the combination is not free of the art, as set forth below.

Applicant's election of species of follicle stimulating hormone (FSH) with traverse in the reply filed on September 25, 2006 is acknowledged. The traversal is on the ground(s) that searching all the species would not impose a serious burden on the office.

The restriction between species is maintained. The Applicant's arguments are not found persuasive because the generic claims 46 and 65 recite a genus comprised of

a multiplicity of species, further comprising variants of follicle stimulating hormone and luteinising hormone that an unduly extensive and burdensome search would be necessary to search every variant covered by the scope of the claim. Further, while the Applicant has provided a disclosure of the relationship between the species as being variants of follicle stimulating hormone or luteinising hormone, this is not enough to make them distinct. While the species of human follicle stimulating hormone and luteinizing hormone share the alpha subunit, the beta subunit is unique to follicle stimulating hormone and is responsible for its biological activity with its receptor. Further, the distinct variants as represented by urinary human follicle stimulating hormone, human follicle stimulating hormone, urinary human luteinizing hormone and recombinant human luteinizing hormone are heterogenous in sequence that result from amino acid substitutions between subunits, that do not overlap and would require a different field of search. Hence, by virtue of the divergent field of search, the species of the variants of follicle stimulating hormone and luteinizing hormone are distinct.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's elected species is not free of the prior art and claims 46-89 that read on the species stand rejected under 35 USC 103 as set forth below.

Claims 46-89 are pending.

Claims 90-107 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species to which the search was not extended,

there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on September 25, 2006.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 46-50, 57-60, 63-64, rejected under 35 U.S.C. 103(a) as being unpatentable over Skrabanja et al (USPN 5,929,028) in view of Koll et al (USPN 6,346,274).

Instant Claims are drawn to a liquid pharmaceutical composition comprising follicle stimulating hormone, a diluent and one surfactant selected from the group consisting of Pluronic F68, further comprising sucrose and methionine.

Skrabanja et al disclose liquid formulations, preferably solutions containing water and small amounts of water miscible solvents (as in instant claims 63-64), such as ethanol (Column 8, lines 55-60) with a pH of about 7.0 (as in the instant claims 59-60, Column 5, lines 42-45), comprising the gonadotropin, follicle stimulating hormone (as in instant claim 46, Column 4, lines 9-10, claim 9), further comprising one or more nonionic surfactants, such as Polysorbate 20, Tween 20, Polysorbate 80, Tween 80 and Pluronic F123 (Column 5, lines 23-25, Table 1). Further, Skrabanja disclose the incorporation of a non-reducing disaccharide, such as sucrose (as in instant claim 57) and a thiother stabilizer, such as methionine (as in instant claim 58, Column 5, lines 1-5, Table 1). Additionally, Skrabanja et al disclose that a useful dosage range for FSH is from about 25-1500 International Units (IU) (Column 6, lines 22-25) and the formulations that comprise the gonadotropin derivative have a suitable concentration in the range 50 to 600 IU/mL (as in the instant claims 47-49, Table I). Skrabanja do not disclose a liquid composition comprising the surfactant Pluronic F68.

Koll et al disclose pharmaceutical compositions wherein the active substance is a physiologically active polypeptide selected from a group comprising EPO, and FSH, further comprising additives, such as detergents selected from the genus of Pluronic (Column 4, line 40) and Tween 20, and disaccharides such as sucrose and trehalose

(Column 4, lines 1-3). Further, Koll et al disclose the influence of aggregates, such as the species of Pluronic F68 (as in the instant claim 50) in a composition with EPO (Example 1, Table 1). Koll et al do not disclose an example of a liquid composition comprising follicle stimulating hormone, and the additive Pluronic F68.

It would have been obvious to one of ordinary skill in the art to interchangeably use the additive Pluronic F68, that belongs to the disclosed genus of Pluronic surfactants with the polypeptide of follicle stimulating hormone in a liquid composition. Koll et al remedies the deficiency of Skrabanja et al, regarding rendering obvious all components of the composition, with the exception that Koll et al uses EPO versus FSH, which is taught by Skrabanja et al in a liquid composition.

5. Claims 51-56, 61-62, rejected under 35 U.S.C. 103(a) as being unpatentable over Skrabanja et al (USPN 5,929,028), and Koll et al (USPN 6,346,274) as applied to claims 46-50, 57-60, 63-64 above, and further in view of Hoffmann et al (EP 0974359, as cited in the Information Disclosure Statement submitted May 21, 2006).

Instant Claims are drawn to liquid pharmaceutical composition comprising variants of follicle stimulating hormone, a diluent and one surfactant selected from the group consisting of Pluronic F68, further comprising m-cresol in an aqueous buffer further comprising sucrose and methionine.

Skrabanja et al and Koll et al disclose liquid pharmaceutical compositions comprising follicle stimulating hormone (600 IU/mL), a diluent, sucrose (50 mg/mL),

methionine (0.1 mg/mL), and a surfactant selected from a group consisting of Pluronic F68 (0.5 % of the particle weight). Skrabanja et al and Koll et al do not disclose liquid pharmaceutical compositions comprising variants of follicle stimulating hormone (as in instant claims 52-53), nor do Skrabanja et al and Koll et al teach bacteriostatic agents selected from a group consisting of phenol and m-cresol (as in instant claims 54-56). Further, Skrabanja et al and Koll et al do not teach liquid pharmaceutical compositions comprising all the above-mentioned additives in one composition (as in instant claims 61-62).

Hoffmann et al disclose FSH and FSH variant formulations in the treatment of fertility disorders for human pharmaceutical use (Page 3, paragraph 13) comprising human urinary follicle stimulation hormone in PBS buffer comprising the preservative m-cresol in an amount of 3.5 mg/mL (as in instant claims 52, 54-56, Page 22, Example 6, also Page 3, paragraph 16). Further, Hoffmann et al also disclose FSH variants such as recombinant human FSH, as variants well known in the art (as in instant claim 53; Page 3, paragraph 10) and formulations that can be prepared comprising the FSH variants, additives such as solubilizers selected from Pluronic F68, preservatives selected from m-cresol, and other excipients, such as sucrose (Page 15, paragraphs 79-82). Hoffmann et al do not disclose any examples teaching compositions comprising a FSH variant and Pluronic F68.

It would have been obvious to one of ordinary skill in the art to combine the formulations of FSH variants with m-cresol as a preservative and pluronic F68 as a surfactant, or to combine the formulations of FSH variants with all the above-mentioned

additives comprising m-cresol, sucrose, methionine and Pluronic F68 in a liquid composition. It is known in the art that preservatives are added to commercially viable formulations to act as anti-microbial, anti-fungal and/or antibacterial agents. It is also known in the art that heterodimeric protein hormones tend to aggregate, and the presence of additives such as Pluronic F68 is advantageous to lower the aggregate formation. Therefore Hoffmann et al with its disclosure of FSH variants remedies the deficiency of Skrabanja et al and Koll et al, regarding Skrabanja and Koll et al's rendering obvious all components of the pharmaceutical composition.

6. Claims 65-71, 75-78, 82-85, 88-89 rejected under 35 U.S.C. 103(a) as being unpatentable over Skrabanja et al (USPN 5,929,028) in view of Koll et al (USPN 6,346,274).

Instant Claims are drawn to a liquid pharmaceutical composition comprising a combination of follicle stimulating hormone and luteinising hormone, a diluent and one surfactant selected from the group consisting of Pluronic F68, further comprising sucrose and methionine.

Skrabanja et al disclose liquid formulations, preferably solutions containing water and small amounts of water miscible solvents (as in instant claims 88-89), such as ethanol (Column 8, lines 55-60) with a pH of about 7.0 (as in the instant claims 84-85, Column 5, lines 42-45), comprising follicle stimulating hormone and luteinizing hormone (as in instant claim 65, Column 6, lines 42-45, claim 11), further comprising one or more

nonionic surfactants, such as Polysorbate 20, Tween 20, Polysorbate 80, Tween 80 and Pluronic F123 (Column 5, lines 23-25, Table 1). Further, Skrabanja disclose the incorporation of a non-reducing disaccharide, such as sucrose (as in instant claim 82) and a thiother stabilizer, such as methionine (as in instant claim 83, Column 5, lines 1-5, Table 1). Additionally, Skrabanja et al disclose that a useful dosage range for FSH is from about 25-1500 International Units (IU) (Column 6, lines 22-25) and the formulations that comprise the gonadotropin derivative have a suitable concentration in the range 50 to 600 IU/mL (as in the instant claims 66-68, Table I). Skrabanja do not disclose a liquid composition comprising the surfactant Pluronic F68.

Koll et al disclose pharmaceutical compositions wherein the active substance is a physiologically active polypeptide selected from a group comprising EPO, FSH and LH, further comprising additives, such as detergents selected from the genus of Pluronic (Column 4, line 40) and Tween 20, and disaccharides such as sucrose and trehalose (Column 4, lines 1-3). Further, Koll et al disclose the influence of aggregates, such as the species of Pluronic F68 (as in the instant claim 71) in a composition with EPO (Example 1, Table 1). Koll et al do not disclose an example of a liquid composition comprising a combination of follicle stimulating hormone and luteininzing hormone, and the additive Pluronic F68.

It would have been obvious to one of ordinary skill in the art to interchangeably use the additive Pluronic F68, that belongs to the disclosed genus of Pluronic surfactants with the polypeptide combination of follicle stimulating hormone and luteinizing hormone in a liquid composition. Koll et al remedies the deficiency of

Skrabanja et al, regarding rendering obvious all components of the composition, with the exception that Koll et al uses EPO versus FSH, which is taught by Skrabanja et al in a liquid composition.

7. Claims 79-81, 86-87, rejected under 35 U.S.C. 103(a) as being unpatentable over Skrabanja et al (USPN 5,929,028), and Koll et al (USPN 6,346,274) as applied to claims 46-50, 57-60, 63-64 above, and further in view of Hoffmann et al (EP 0974359).

Instant Claims are drawn to liquid pharmaceutical composition comprising a combination of follicle stimulating hormone and luteinizing hormone, a diluent and one surfactant selected from the group consisting of Pluronic F68, further comprising m-cresol in an aqueous buffer further comprising sucrose and methionine.

Skrabanja et al and Koll et al disclose liquid pharmaceutical compositions comprising a combination of recombinant follicle stimulating hormone (600 IU/mL) and luteinizing hormone, a diluent, sucrose (50 mg/mL), methionine (0.1 mg/mL), and a surfactant selected from a group consisting of Pluronic F68 (0.5 % of the particle weight). Skrabanja et al and Koll et al do not disclose liquid pharmaceutical compositions comprising bacteriostatic agents selected from a group consisting of phenol and m-cresol (as in instant claims 79-81). Further, Skrabanja et al and Koll et al do not teach liquid pharmaceutical compositions comprising all the above-mentioned additives in one composition (as in instant claims 86-87).

Hoffmann et al disclose FSH formulations in the treatment of fertility disorders for human pharmaceutical use (Page 3, paragraph 13) comprising the preservative m-cresol in an amount of 3.5 mg/mL (as in instant claims 79-81, Page 22, Example 6, also Page 3, paragraph 16). Hoffmann et al do not disclose any examples teaching compositions comprising a combination of FSH, LH and Pluronic F68.

It would have been obvious to one of ordinary skill in the art to combine the combined formulation of FSH and LH with m-cresol as a preservative and pluronic F68 as a surfactant, or to combine the combined formulations of LH and FSH with all the above-mentioned additives comprising m-cresol, sucrose, methionine and Pluronic F68 in a liquid composition. It is known in the art that preservatives are added to commercially viable formulations to act as anti-microbial, anti-fungal and/or antibacterial agents. It is also known in the art that heterodimeric protein hormones tend to aggregate, and the presence of additives such as Pluronic F68 is advantageous to lower the aggregate formation. Therefore Hoffmann et al with its disclosure of preservatives remedies the deficiency of Skrabanja et al and Koll et al, regarding Skrabanja and Koll et al's rendering obvious all components of the pharmaceutical composition.

With regards to the ratios of follicle stimulating hormone to luteinizing hormone (as in the instant claims 75-78), it would have been obvious to one of ordinary skilled in the art at the time of the invention to determine all operable and composition ratios in the claimed combined composition of Skrabanja et al because the composition ratios

are an art-recognized result-effect variable that is routinely determinable and optimized in the composition arts.

Claim Objections

8. Claims 72-74 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hemant Khanna
October 26, 2006

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